REMARKS

Claims 1-68 are pending in this application. Claim 35 has been allowed. Claims 38-68 are newly presented. Claims 37-68 are directed to antibacterial agents comprising, as an active ingredient, penem derivatives or pharmacologically acceptable salts thereof according to Claims 1-32. In view of the claims as they now stand, together with the remarks hereunder, the Applicants believe that the claims are in condition for allowance.

The Examiner required election of a single disclosed species for search purposes only. The Applicants' representative elected with traverse on April 28, 1997 the compound of Example 111 (page 264-265 of the specification) as the species. Election of this species for search purposes only is confirmed. The Examiner indicated in a telephonic interview with the Applicants' representative, Mr. John Pike, on November 4, 1997, that there is no restriction requirement in the present application, and that the Examiner expanded his search and examined the full scope of all of the pending claims. The Applicants' representative thanks the Examiner for expanding the search and for examining all of the claims on the merits.

The present invention concerns penem compounds in the cis configuration which are useful as antibacterial agents. The rejections of the claims under 35 U.S.C. §103(a) are respectfully traversed.

Afonso et al discloses compounds which have a 1-hydroxyethyl group as a 6-substituent while the present compounds do not. Also, Afonso et al discloses penem compounds which are (5R,6S,8R, i.e., 1'R,5R,6S) compounds (i.e., trans compounds). Furthermore, the specific examples given in Afonso et al are (5R,6S,8R) isomers. Moreover, the process disclosed in Afonso et al cannot result in the synthesis of the cis compounds

(columns 3-4).

Girijavallabhan et al discloses compounds which have a 1-hydroxyethyl group as a 6-substituent while the present compounds do not. Furthermore, Girijavallabhan et al states that "5R isomers are entirely responsible for the observed activity" (i.e., antibacterial activity) (page 3487, last paragraph). Since the present specification demonstrates that the present cis compounds have antibacterial activity, the present compounds are distinguishable from the disclosure of Girijavallabhan et al.

Ishiguro et al relates to a process for the preparation of cis-form penems by irradiation with light. The compounds of Ishiguro et al contain a 1-hydroxyethyl group as a 6-substituent and a methoxymethyl group or tetrahydrofuranyl group as a 2-substituent. However, in connection with cis-form compounds, Ishiguro et al fails to suggest the advantageous effects of the present compounds.

Each compound disclosed in Sunagawa et al contains a 1-hydroxyethyl group as a 6-substituent. Sunagawa et al discloses a cis-form compound, but (5R,6R,8S) is disclosed merely as one of the combinations. Specifically, (5R,6R,8R) and (5R,6S,8R) are disclosed as most preferred embodiments (column 7, lines 42-63), but such a suggestion is not made with respect to (5R,6R,8S).

In Menard et al, hydroxy-substituted lower alkyl groups are referred to as preferred examples of the 6-substituent (column 13, lines 56-59). Of these groups, α-hydroxyethyl is described to be most preferable (column 13, lines 63-64). There is accordingly no suggestion to the effect that hydroxypropyl is particularly advantageous. In fact, Menard et al indicate in column 427 that the compounds containing at their 6-positions substituents greater than propyl, namely, the compound of Example 93 (column 342), the compound of Example 94

(column 348) and the compound of Example 95 (column 353) have antibacterial activities inferior to the hydroxylethyl-substituted compound. Concerning steric configuration, isomer B, namely, (1'R,5R,6S) and (1'S,5S,6R) are described as preferred configurations (column 12, lines 48-49). However, Menard et al contain no suggestion about whether or not (1'S,5R,6R) is advantageous.

Gosteli et al disclose various substituent groups as 6-substituents, including 1-hydroxypropyl (column 20, lines 19-20). Gosteli et al however do not disclose any specific compound containing a 1-hydroxypropyl group. Concerning steric configuration, the 5R-configuration corresponding to natural penicillin is disclosed (column 16, lines 53-60). However, Gosteli et al do not contain any disclosure to the effect that the cis form is advantageous. The specific production process and working examples disclosed in Gosteli et al are limited only to trans forms.

Leanza et al discloses 6-(l-hydroxypropyl) as a preferred example (column 18, line 26). However, in column 20 where relationships between steric configurations and 6-substituents are disclosed, it is only the trans-form compound (lines 13-20) that contains 1-hydroxypropyl as a preferred 6-substituent, and 1-hydroxypropyl is not included in preferred illustrative 6-substituents for cis forms. From this, the compounds of Examples 83-89 in column 45 are gathered to be trans forms.

In regard to the 35 U.S.C. §102(b) rejection over Minamida et al, the Examiner asserts that among the present compounds, those containing 1-methyltetrazol-5-ylthio as R^1 are disclosed in Minamida et al. The Examiner is however believed to have intended 1-methyltetrazol-5-ylthiomethyl instead of the above substituent. However, the steric configuration of 1'-hydroxy is not disclosed in the compounds disclosed in Minamida et al.

In regard to the 35 U.S.C. §103(a) rejection over Minamida et al, this reference discloses a compound containing a 1-hydroxyalkyl group as a 6-substituent, and one of the working examples is directed to a compound containing 1-hydroxypropyl. In Minamida et al, it is not indicated that 1-hydroxypropyl is particularly advantageous.

Significantly lower antibacterial activities of a compound containing a 1-hydroxypropyl group at its 6-position compared with that containing a 1-hydroxyethyl group at its 6-position are also disclosed in JP Kokai 60-222486 in the name of Bristol-Myers Co. cited in the International Search Report.

As the technical standard on the steric configurations of penem compounds at the time of the filing of the present application, Hiraoka et al reported that a penem compound with a 6-hydroxyethyl group of the same configuration as that in thienamycin (8R,5,6-trans) shows strong antibacterial activities, the 8S,5,6-trans form has weak antibacterial activities, and the 8R,5,6-cis form exhibits substantially no antibacterial activities against Gram-negative bacteria [YAKUGAKU ZASSHI, 107(3), 175-191 (1987)].

Moreover, the disclosures in the cited references are limited to such extent that the 6-hydroxypropyl group is merely referred to as one of various substituents and (1'S,5R,6R) is merely referred to as one of the possible steric structures or as one of the isomers in a mixture. In view of the findings and knowledge available at the time of the filing of the present application and the technical common knowledge available from these cited references that antibacterial activities vary substantially depending on the substituent and its steric configuration, it is not believed to have been possible to infer the present compounds each of which features the specific combination of the 6-(1-hydroxypropyl) group and the steric configuration (1'S,5R,6R).

In the cited references, a comparison between the 6-hydroxypropyl group and the 6-hydroxyethyl group indicates that they are different in activities although they are similar in structure. Further, the cited references indicate the superiority of the 6-hydroxyethyl group or are directed toward compounds each of which contains a 6-hydroxyethyl group. A similar conclusion can also be derived with respect to the steric configuration. The cited references indicate the superiority of (1'R,5R,6S) or are directed toward this configuration. Namely, the cited references fail to give sufficient motivation for one toward the specific combination in the present invention, that is, to combine 6-hydroxypropyl and (1'S,5R,6R) together.

The specific combination in the present invention was found for the first time by the present inventors who had antibacterial activities against MRSA as a theme in mind, and should not have been suggested no matter how the cited references were combined. As a matter of fact, the specific combination is believed to be taught away by any combination of the cited references.

The Applicants submit that the present invention is now in condition for allowance.

Early notification of such action is courteously solicited.

Respectfully submitted,

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